Getting balance: Drugs for bipolar disorder share target

Lithium and anticonvulsants such as valproic acid have the same end result: a more stable life for people with bipolar disorder. Now it seems they may also affect the same biochemical pathway in the brain.

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Lithium and valproic acid (VPA) are the major treatment options for bipolar disorder (BP, or manic depression). Yet still little is known about their mechanism of therapeutic action. In the May 16 issue of *Nature*[1], Williams *et al.* use a novel tissue-culture assay that measures sensory neuron growth-cone stability to infer that mood stabilizers have a common mechanism of action—depletion of neuronal inositol (1,4,5) trisphosphate (IP_3). These findings reinvigorate a proposal originally made by Berridge *et al.*[2] over a decade ago based upon the observation that lithium, one of the best characterized mood stabilizers, inhibits the dephosphorylation of IP_3 at therapeutic concentrations, thereby depleting cells of free inositol.

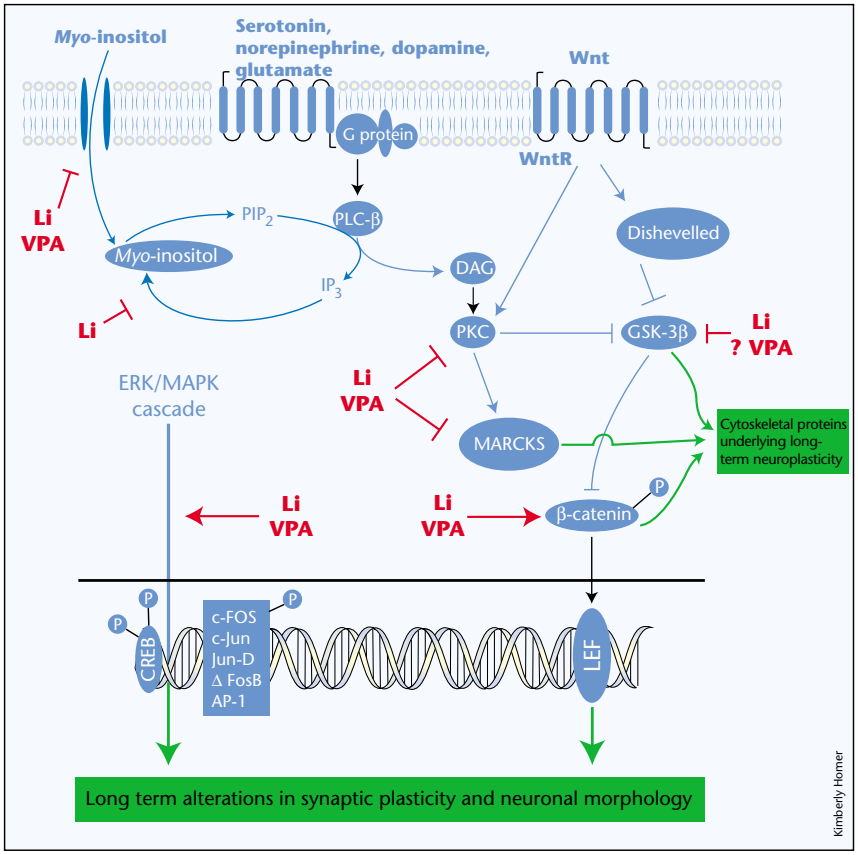

Fig. 1 Intracellular signaling cascades involved in long term stabilization of mood by lithium (Li) and valproic acid (VPA). Activation of receptors coupled to PI hydrolysis results in the breakdown of phosphoinositide 4,5-biphosphate (PIP_2) into two second messengers: IP_3 and diacylglycerol (DAG), which is an endogenous activator of PKC. Lithium is an uncompetitive inhibitor of inositol monophosphatases, whereas both lithium and VPA, upon chronic administration, decrease *myo*-inositol uptake. These perturbations by mood stabilizers likely contribute to the reduction in PKC activity and the reduced levels of PKC-α, PKC-ε and myristoylated alanine-rich C kinase substrate (MARCKS), a major PKC substrate in the CNS, that occur after chronic exposure to lithium or VPA. One pathway gaining attention in the adult mammalian brain is the Wnt signaling pathway. Binding of the Wnt signal to the Wnt receptor (WntR) activates an intermediary protein, 'disheveled', which regulates GSK-3β. GSK-3β regulates cytoskeletal proteins, and also has an important role in determining cell survival and cell death. Lithium (and possibly VPA) directly inhibit GSK-3β, which may underlie, at least in part, the increases in β-catenin that occur after chronic treatment with these agents. The ERK MAP kinase cascade regulates several important transcription factors, most notably CREB and activator protein-1 (Ap-1). Recent studies have demonstrated that both lithium and VPA activate the ERK MAP kinase cascade, which may contribute to the long term changes in synaptic plasticity and morphology that follow chronic treatment. Together, the regulation of these signaling pathways brings about an enhancement of synaptic connectivity potentially necessary for long-term stabilization of mood.

Bipolar disorder, which affects 1% of the population, is characterized by episodes of either depression or elevated mood, ranging from mild elation to manic psychosis. These episodes are interspersed with periods of relatively normal mood. Although BP has been linked to creativity, it can be highly disabling and bears a lifetime risk for suicide of 15% when untreated. Twin, adoption and family studies indicate a high degree of heritability, and genome-wide screens have revealed several sites on the human genome that may be linked to BD.

The first effective treatment of BD, lithium salts, was discovered serendipitously over 50 years ago by Cade. As an inorganic cation, lithium differs from most other psychotropic medications, which generally affect specific neurotransmitter systems such as dopamine receptors (for antipsychotics) or serotonin transporters (for antidepressants). Furthermore, lithium does not act as an anti-depressant or anti-manic agent, instead it stabilizes mood by reducing the incidence of episodes of severe depression and manic psychosis. Indeed these episodes may often require treatment with antidepressants or antipsychotics, respectively, in addition to lithium. More recently, the anticonvulsant VPA has been shown to be an effective mood stabilizer. Other anticonvulsants such as carbamazepine and lamotrigine also show promise as mood stabilizers.

As there is little evidence that lithium or anticonvulsants alter spe-

cific neurotransmitter function, how can their mechanism of action be elucidated? The strategy used by Williams *et al*. and several other investigators is to identify a presumed final common pathway of action that is affected by lithium, VPA and possibly carbamazepine, which are structurally dissimilar compounds. However, a major challenge is the attribution of therapeutic relevance to any observed biochemical finding. To validate the target, several criteria should ideally be met. The biochemical effects must occur at therapeutically relevant concentrations, after chronic administration, and they should affect neuronal systems that are plausibly involved in mood regulation[3,4]. With the advances in the genetic studies, the affected pathway might also be tethered to risk genes identified for BD (ref. 5).

Current research, including that of Williams *et al*., points to mood stabilizers acting on a family of intracellular signal transduction molecules that alter gene expression, the IP_3 pathway (Fig. 1). To get at this pathway, Williams *et al*. found that mood stabilizers had an effect on neuronal growth cones; like lithium, carbamazepine and VPA increased the spread of growth cones and reduced their collapse. The fact that these drugs affect the neuronal development of the human embryo and fetus[6] suggests that an assay based on growth cones is plausible. Indeed, the authors found that the effects of all three drugs on growth cones were overcome by exogenous *myo*-inositol. A cautionary note in the interpretation of the latter result is the fact that in some other model systems, a compound that is not incorporated into the phosphoinositol (PI) cycle, epi-inositol, also attenuates lithium's effects.

The authors then used the slime mold, *Dictyostelium*, which relies on IP_3 for its development, to identify mutants that confer resistance to the drugs. Null mutations of a gene that encodes a protein of unknown intracellular function, prolyl oligopeptidase, confer lithium resistance and elevate intracellular levels of IP_3. The authors drew a link between their slime-mold studies and mammals by showing that prolyl oligopeptidase inhibitors abolished the effects of lithium, carbamazepine and VPA on growth-cone collapse in mammalian cells. One laboratory has reported that the activity of prolyl oligopeptidase is altered in the blood of patients with BD although changes are not disorder-specific, as they also occur in post-traumatic stress disorder and schizophrenia[7]. Although these findings appear to link the clinical condition and the findings in slime molds, it is unclear whether the association is more than just coincidental; still unknown is how prolyl oligopeptidase affects IP_3 in slime molds and whether the peptidase works in similar ways in humans.

Although none of the target-validating criteria outlined above are absolute, they may help focus research onto the most therapeutically relevant pathways. In this context, the protein kinase C (PKC) signaling cascade meets most of the criteria[3,4]. In fact, tamoxifen (a PKC inhibitor at high concentrations) is currently being investigated as a treatment for mania, with encouraging preliminary results[3]. Extensive investigation is also focused on the signaling molecule glycogen synthase kinase-3 (GSK-3), fueled by the demonstration that lithium inhibits GSK-3 (refs. 6,7) and that both lithium and VPA regulate the GSK-3 signaling cascade.

Recently, neurotrophic signaling cascades have been identified as targets for mood stabilizing agents. Neurotrophic factors were first characterized as regulators of neuronal growth and differentiation, but are now known to also act as potent regulators of plasticity and survival of adult neurons and glia[8]. And, it seems, they may have a role in BD; patients with the disorder show regional reductions in central nervous system (CNS) volume, and reductions in the size and/or number of neurons and glia in discrete areas of the brain[8,9]. In rodents, chronic administration of lithium and VPA activates a major neurotrophic signaling pathway—the ERK (extracellular signal-regulated kinase) MAP (mitogen-activated protein kinase) cascade, and its downstream effectors RSK (ribosomal s6 kinase) and CREB (cAMP response-element binding protein). In the prefrontal cortex—the same brain region disrupted in imaging studies of BD patients—inactivation of the pro-apoptotic protein, BAD, and robust up-regulation of the anti-apoptotic protein Bcl-2 also accompany mood stabilizer activation of ERK (ref. 10).

Evidence from humans for such neurotrophic effects of mood stabilizers comes from imaging studies, which have demonstrated that chronic lithium administration not only increases the levels of *N*-acetylaspartate, a marker of neuronal viability[11], in human brain, but also increases gray-matter volumes in BD patients[3]. One thought is that activation of these neurotrophic signaling cascades serves to enhance synaptic connectivity and provides buffering against the deleterious cellular effects of stress and illness episodes, thereby bringing about a long-term stabilization of mood[3,8].

Williams *et al*. have used a new model to identify a potential mechanism of action of mood stabilizers. If further validated *in vivo*, these observations will add to the body of data identifying CNS intracellular signaling cascades as targets for mood stabilizers, and may ultimately lead to the development of novel, more specific therapies for this devastating illness.

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